1: Dis Markers. 1991 May-Aug;9(3-4):225-31. Related Articles, Li

Antibody directed enzyme prodrug therapy (ADEPT): a three phase system.

Sharma SK, Bagshawe KD, Springer CJ, Burke PJ, Rogers GT, Boden J Antoniw P, Melton RG, Sherwood RF.

Department of Medical Oncology, Charing Cross Hospital, London, U.K.

Monoclonal anti-CEA antibody, A5B7, and its fragments conjugated to CPG localize to a peak concentration in the LS174T xenografts within 24 h after injection, but enzyme activity persists in plasma such that prodrug injection h to be delayed for 5-6 days in order to avoid toxicity. Injection of prodrug at t time did not result in growth delay of this tumour. A three-phase system has been developed in which residual plasma enzyme was inactivated and cleare by a galactosylated anti-CPG2 antibody, SB43gal, allowing prodrug administration within 24 h after the conjugate. Using this three-phase system marked growth delay of this tumour was achieved after a single course of treatment consisting of conjugate injection followed by SB43gal, 19 h later a three doses of the prodrug.

PMID: 1813212 [PubMed - indexed for MEDLINE]

1: Dis Markers. 1991 May-Aug;9(3-4):233-8. Related Articles, Li

Antibody directed enzyme prodrug therapy (ADEPT): clinical report.

Bagshawe KD, Sharma SK, Springer CJ, Antoniw P, Boden JA, Rogers GT, Burke PJ, Melton RG, Sherwood RF.

Department of Medical Oncology, Charing Cross and Westminster Medical School, London.

Following an extensive series of studies in nude mice with human xenografts pilot scale clinical trial of antibody directed enzyme prodrug therapy has bee initiated. The principle is to activate a relatively inert prodrug to an active cytotoxin by a tumour located enzyme. In the first stage of the study a prodru para-N-(mono-2-chloroethyl monomesyl)-aminobenzoyl glutamic acid was administered to six patients with advanced colorectal cancer in a dose escalating protocol. Nausea and vomiting occurred as the only discernible to: effect at the higher dose levels. Three of these patients and two other patients with advanced disease have proceeded to the second stage of the study in wh an antibody-enzyme conjugate was given IV, followed after 36-48 h by a galactosylated anti-enzyme antibody. When plasma enzyme levels had becon undetectable the patients received multiple doses of the prodrug. At the lowe doses toxicity was minimal as were clinical responses. Two patients received higher doses which resulted in myelosuppression and temporary regression o advanced disease. Nó complications resulted from administration of the antibody-enzyme complex or enzyme inactivating antibody. The myelosuppression is attributable to the relatively long half-life of the active drug formed from the prodrug used in the present study.

Publication Types:
- Clinical Trial

PMID: 1813213 [PubMed - indexed for MEDLINE]

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Jun 5 2003 10:(

1: Br J Cancer. 1989 Sep;60(3):275-81. Related Articles, Li

The First Bagshawe lecture. Towards generating cytotoxic agent at cancer sites.

Bagshawe KD.

Department of Medical Oncology, Charing Cross Hospital, London, UK.

Several years of experience have now accumulated in the targeting of anti-cancer agents so that we can take stock, identify problems and look for ways round them. Three major obstacles seem to limit present approaches. These a heterogeneity in the distribution of target molecules within the cancer cell population, the pharmacokinetic characteristics of macromolecules and host antibody response to foreign protein. An approach which we have been investigating uses antibodies or other vectors to carry enzymes which have n close human homologue to tumour sites. After clearing residual enzyme activity from the blood by one of several possible techniques, a relatively noi toxic prodrug is given. This prodrug is a substrate for the tumour located enzyme which results in the generation of a highly toxic molecule able to penetrate the tumour mass and cross cell membranes. Genetic engineering methods now offer the prospect of human immunoglobulins with tumour binding and catalytic sites having the potential to minimise host response. Whether this can be achieved depends on having antibodies with adequate specificity and our ability to develop enzyme-prodrug systems with the required characteristics. Early results encourage us to think progress can be made in this direction.

Publication Types:
- Review
- Review, Academic

PMID: 2675955 [PubMed - indexed for MEDLINE]

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1: Proc Natl Acad Sci U S A. 1988 Jul;85(13):4842-6. Related Articles, Li

Anti-tumor effects of antibody-alkaline phosphatase conjugates combination with etoposide phosphate.

Senter PD, Saulnier MG, Schreiber GJ, Hirschberg DL, Brown JP, Hellstrom I, Hellstrom KE.

Oncogen, Seattle, WA 98121.

Two anti-tumor monoclonal antibodies, L6 (anticarcinoma) and 1F5 (anti-B lymphoma), were covalently linked to alkaline phosphatase (AP), forming conjugates that could bind to the surface of antigen-positive tumor cells. The conjugates were capable of converting a relatively noncytotoxic prodrug, etoposide phosphate (EP), into etoposide--a drug with significant antitumor activity. In vitro studies with a human colon carcinoma cell line, H3347, demonstrated that while EP was less toxic than etoposide by a factor of great than 100, it was equally toxic when the cells were pretreated with L6-AP, a conjugate that bound to the surface of H3347 cells. The L6-AP conjugate localized in H3347 tumor xenografts in nude mice and histological evaluatio indicated that the targeted enzyme (AP) was distributed throughout the tumo mass. A strong antitumor response was observed in H3347-bearing mice that were treated with L6-AP followed 18-24 hr later by EP. This response, whicl included the rejection of established tumors, was superior to that of EP (P les than 0.005) or etoposide (P less than 0.001) given alone. The IF5-AP conjug did not bind to H3347 cells and did not enhance the toxicity of EP on these cells in vitro. In addition, IF5-AP did not localize to H3347 tumors in nude mice and did not demonstrate enhanced antitumor activity in combination wi the prodrug.

PMID: 3387440 [PubMed - indexed for MEDLINE]

1: Proc Natl Acad Sci U S A. 1992 Aug 1;89(15):6871-5.

Secretion of a soluble, chimeric gamma delta T-cell receptor-immunoglobulin heterodimer.

Eilat D, Kikuchi GE, Coligan JE, Shevach EM.

Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.

Soluble derivatives of T-cell antigen receptors (TCRs) should prove invaluat for studying the interaction of these receptors with antigens and major histocompatibility complex molecules, for structural studies, and for the identification of unknown ligands. We have engineered chimeric proteins, containing the extracellular domains of the mouse V gamma 1.1-C gamma 4 and V delta 6.2-C delta (V, variable; C, constant) TCR chains fused to the hinge region, CH2 (H, heavy), and CH3 domains of human IgG1 heavy chai and expressed them by transient transfection in COS cells. We show here tha TCR gamma-IgH and TCR delta-IgH chimeric chains are produced intracellularly in significant amounts, that the two chains can assemble correctly to form disulfide-linked, glycosylated heterodimers, and that a selective mechanism allows secretion of correctly paired receptor chains into the medium. Identity of the chimeric secreted TCR gamma delta-IgH heterodimer was confirmed by immunoblot analysis using V gamma 1-specil anti-peptide antiserum and immunoprecipitation analysis using the monoclor antibody UC7, which is shown to be specific for the TCR delta chain. In addition, the soluble TCR gamma delta-IgH heterodimer can be immunoprecipitated with the anti-clonotypic monoclonal antibody F10/56, which suggests that the fusion protein likely has a structural conformation similar to that of the native TCR. The COS cell expression system may prove useful for the production of additional TCR-IgH fusion proteins.

PMID: 1495977 [PubMed - indexed for MEDLINE]